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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Jeffrey R. Sampson

Serial No.: 09/358,141

Examiner: Zara, Jane J.

Filing Date: July 20, 1999

Group Art Unit: 1635

Title: Method of Producing Nucleic Acid Molecules with Reduced Secondary Structure

COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

Sir:

Transmitted herewith is the Appeal Brief in this application with respect to the Notice of Appeal filed on December 8, 2005.

The fee for filing this Appeal Brief is (37 CFR 1.17(c)) \$500.00.

(complete (a) or (b) as applicable)

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136(a) apply.

☐ (a) Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)(1)-(5)) for the total number of months checked below:

<input type="checkbox"/>	one month	\$ 120.00
<input type="checkbox"/>	two months	\$ 450.00
<input type="checkbox"/>	three months	\$1020.00
<input type="checkbox"/>	four months	\$1590.00

☐ The extension fee has already been filled in this application.

☒ (b) Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

Please charge to Deposit Account 50-1078 the sum of \$500.00. At any time during the pendency of this application, please charge any fees required or credit any overpayment to Deposit Account 50-1078 pursuant to 37 CFR 1.25.

A duplicate copy of this transmittal letter is enclosed.

Respectfully submitted,

Jeffrey R. Sampson

By

*Cynthia J. Lee*  
Cynthia J. Lee  
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Reg. No. 46,033

Date: 02/08/06

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☐ I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Date of Facsimile: February 8, 2006

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Rev 10/04 (Apr 05)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BOARD OF PATENT APPEALS AND INTERFERENCES

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In Re Application of:	)	
Jeffrey R. Sampson	)	Art Unit: 1635
Serial No.: 09/358,141	)	Examiner: Zara, James J.
Filed: July 20, 1999	)	Docket No. 10990393-1
	)	(TKHR Docket No.: 50113-1280)
For: Method of Producing Nucleic Acid Molecules with Reduced Secondary Structure	)	Appeal No.: _____

APPEAL BRIEF UNDER 37 C.F.R. §41.37

Mail Stop: Appeal Brief-Patents  
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Alexandria, VA 22313-1450

Sir:

This Appeal Brief under 37 C.F.R. § 41.37 is submitted in support of the Notice of Appeal filed December 8, 2005, which Brief responds to the final Office Action mailed June 13, 2005 and the Advisory Action mailed December 22, 2005.

It is not believed that extensions of time or fees are required to consider this Appeal Brief. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to Deposit Account No. 50-1078.

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### **I. Real Party in Interest**

The real party in interest of the instant application is Agilent Technologies, Inc., a Delaware corporation, having a principal place of business in Loveland, Colorado.

### **II. Related Appeals and Interferences**

There are no known related appeals or interferences that will affect or be affected by a decision in this Appeal.

### **III. Status of Claims**

Claims 1 and 25-35 stand finally rejected. Claims 2-24 are canceled. No claims have been allowed. The final rejections of claims 1 and 25-35 are appealed.

### **IV. Status of Amendments**

A Final Office Action issued on June 13, 2005 in which claims 1 and 25-35 were rejected; claims 1-18 stood withdrawn from consideration. In a Response to the Final Office Action filed on August 15, 2005, claims 10-18 were canceled. In an Advisory Action mailed December 22, 2005, the Examiner entered the cancellation of claims 10-18.

All of the above-identified amendments have been entered and no other amendments have been made to any of the claims. The claims in the attached Claims Appendix (see below) reflect the present state of those claims.

#### **V. Summary of Claimed Subject Matter**

The subject matter described in the following appears in the original disclosure at least where indicated, and may further appear in other places within the original disclosure. In one aspect, the present invention provides for a method of producing an unstructured nucleic acid, comprising the steps of i) providing a nucleic acid template including a first nucleic acid sequence and a second nucleic acid sequence substantially complementary to said first nucleic acid sequence; ii) providing nucleic acid precursors to produce said unstructured nucleic acid which is complementary with said first and second nucleic acid sequences, said nucleotide precursors being unable to hybridize with complementary nucleotide precursors; and iii) contacting said nucleic acid template and said nucleotide precursors with an enzyme under conditions such that said unstructured nucleic acid is produced. *Specification* at page 7, lines 4-11.

The present invention also provides for a method described in the preceding paragraph wherein the nucleic acid precursors comprise at least two nucleotides capable of being incorporated enzymatically into a polynucleotide, and wherein said at least two nucleotides are unable to form intramolecular base pair but can form intermolecular base pairs. *Specification* at page 7, lines 12-15.

In one aspect, the present invention provides a method of producing nucleic acid molecules with reduced levels of intramolecular base pairing by incorporating nucleotides having modified bases such that complementary bases in a nucleic acid molecule are unable to form stable hydrogen bond base pairs. A modified base pair may comprise one modified base and one natural base, or it may comprise two modified bases. Preferably, modified bases are positioned in nucleic acid molecules of the present invention in sequence elements of substantially complementary sequence to reduce intramolecular base pairing. Nucleic acid

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molecules of the present invention are produced by any method. *Specification* at page 4, lines 3-10.

In yet another preferred embodiment, nucleic acid molecules with reduced levels of secondary structure are produced by chemical synthesis or enzymatic synthesis. Preferably, nucleic acid molecules of the present invention are produced enzymatically. *Specification* at page 5, lines 22-24.

#### **VI. Grounds of Rejection to be Reviewed on Appeal**

The following issue presents the ground of rejection to be reviewed on appeal: whether claims 1 and 25-35 are anticipated under 35 U.S.C. §102(e) by *Vivekananda et al.* (U.S. Patent 6,569,630, "*Vivekananda*") and *Kutyavin et al.* (U.S. Patent 5,912,340, "*Kutyavin*").

#### **VII. Arguments**

Applicant respectfully submits that claims 1 and 25-35 are allowable over *Vivekananda* and *Kutyavin*.

Applicant respectfully requests that the Board of Patent Appeals overturn the final rejections of those claims for the reasons discussed below.

##### **A. Claim 1 is Patentable over *Vivekananda***

Claims 1 and 25-34 are rejected under 35 U.S.C. 102(e) as being anticipated by *Vivekananda*. Applicant traverses this rejection for at least the reason that *Vivekananda* does not teach or suggest at least the step of claim 1 of "providing a collection of nucleotides ..., the collection including at least a first complementary nucleotide that hybridizes with a first

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residue within the first sequence element on the template strand and a second complementary nucleotide that hybridizes with a second residue within the second sequence element on the template strand, wherein the first and second residues are complementary to one another but the first and second nucleotides have a reduced ability to form a stable hydrogen bonded base pair.” In the Advisory Action mailed December 22, 2005, the Examiner responds to Applicant’s previous arguments by asserting the following:

In columns 20-24, 29-31, Vivekananda et al. teach the synthesis of nucleic acid ligands that contain modified nucleotides that render intra-strand, complementary nucleotides with a reduced ability to form stable hydrogen bonded base pairs.

*Advisory Action* at 2. Applicant respectfully traverses. For example, in cols. 20-21, *Vivekananda* simply provides a laundry list of various modified nucleotide bases, but still does not provide for the step of claim 1 recited above.

In addition, the *Advisory Action* states that “the fact that aptamers are a preferred embodiment does not preclude *Vivekananda* as prior art of the instantly claimed invention.” *Advisory Action* at 2. Applicant traverses because the feature of claim 1 recited above is not taught by the aptamer embodiment of *Vivekananda*. Indeed, at the cols. 29-31 of *Vivekananda* cited by the Office, the nucleic acid ligands to be used are consistently referred to as aptamers. *See, e.g.*, col. 29, lines 32-33, 39, 56-59, 63-67 and col. 30, lines 1-3. *Vivekananda* describe their nucleic acids as aptamers, that is “a nucleic acid that binds to another molecule (‘target’ as defined below). This binding interaction does not encompass standard nucleic acid/nucleic acid hydrogen bond formation ....” *Vivekananda*, col. 8, lines 27-33 (emphasis added). Additionally, and very importantly, *Vivekananda* specifically defines its “nucleic acid ligands” in a manner that specifically excludes the feature of claim 1 recited above. *Vivekananda* states the following:

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*The meaning of "nucleic acid ligand" specifically excludes nucleic acids that bind to another nucleic acid through a mechanism which predominantly depends on Watson/Crick base pairing.*

*Vivekananda*, col. 8, lines 4-7 (emphasis added). In contrast, as noted above, claim 1 recites:

"a collection of nucleotides ..., the collection including at least a first complementary nucleotide that hybridizes with a first residue within the first sequence element on the template strand and a second complementary nucleotide that hybridizes with a second residue within the second sequence element on the template strand...; and ... polymerize the nucleotides under conditions and for a time sufficient to synthesize an unstructured nucleic acid." Clearly, the unstructured nucleic acid recited in claim 1 is not anticipated by the nucleic acid ligand of *Vivekananda* because the unstructured nucleic acid of claim 1 is comprised of nucleotides that are capable of hybridizing to a template strand.

No where does *Vivekananda* teach or suggest first and second residues that are complementary to one another but have a reduced ability to form a stable hydrogen bonded base pair, as recited in claim 1. In addition, *Vivekananda* does not teach or suggest an unstructured nucleic acid in which two complementary nucleotides of the unstructured nucleic acid do not form an intramolecular base pair, as recited in claim 1. For at least these reasons, the rejection is misplaced and should be withdrawn.

**B. Claims 1 is Patentable over *Kutyavin***

Claims 1 and 25-35 are rejected under 35 U.S.C. 102(e) as being anticipated by *Kutyavin*. Applicant respectfully traverses for at least the reason that *Kutyavin* does not teach or suggest at least *any* of the steps of claim 1.

Attached as Exhibit "A" are three schemes that Applicant has developed to help elucidate the present claims in view of the prior art and demonstrate the novelty and

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nonobviousness of the claims in view of the prior art. As illustrated in Scheme A, prior to *Kutyavin*, strand invasion of double-stranded DNA or RNA was typically accomplished via the incorporation of a single strand of an oligonucleotide into the double-stranded DNA or RNA. As demonstrated in Scheme B, *Kutyavin* discloses *a matched set of oligonucleotides* containing modified nucleotides, where each member of the set is able to hybridize with a complementary strand in a *duplex nucleic acid molecule*, but is unable to hybridize with the other member of the matched set. Support for the characterization of the teachings of *Kutyavin* as illustrated in Scheme B can be found in at least the following passages of *Kutyavin*:

In accordance with the present invention *a matched pair of oligonucleotides* (ODNs) are provided where each member of the pair is complementary or substantially complementary in the Watson Crick sense to a *target duplex sequence*.... The ODNs of the invention... form substantially stable hybrids with the target sequence *in each strand of duplex nucleic acid*.

The ODNs of the present invention are termed Selective Binding Complementary (SBC) ODNs....

[A] key feature of the SBC ODNs of the present invention is that *each* one of a matched pair of the SBC ODNs is complementary, or substantially complementary, to one target sequence in *duplex* nucleic acid wherein the target sequences are themselves complementary or substantially complementary to one another, and each one of the matched pair of SBC ODNs forms a stable hydrogen bonded hybrid with one strand of the target sequence.... *Thus, the SBC ODNs are not hybridized to one another but they readily hybridize, especially ... when the target is in long double stranded DNA, with both strands of the target sequence.*

*Kutyavin* at col. 1, lines 39-67 and col. 2, lines 14-31 (emphasis added). In addition,

*Kutyavin* refers to the modified SBC nucleotides at the following passage:

*A sufficient number of the modified SBC nucleotides are incorporated such that complementary positions in both SBC ODNs are modified into a matched pair of SBC ODNs of the present invention so that the pair of the matched set does not form a stable hybrid*.... It is not necessary to replace each natural nucleotide of the ODN with a modified SBC nucleotide in order to accomplish this. Both members of the matched pair are however



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complementary to a target sequence in double stranded or duplex nucleic acid, where the two strands or parts of the target duplex are themselves complementary or substantially complementary to one another. As it is described in more detail below, an important use of the SBC ODNs of the present invention is hybridization with secondary structure of mRNA wherein the mRNA itself forms a duplex, such as in hairpin loops.... The general concept of double stranded DNA and of secondary structure in mRNA and ribosomal RNA is covered in this description by the term "duplex nucleic acid".

*Kutyavin* at col. 4, lines 39-67 (emphasis added). In this passage, *Kutyavin* is referring to the formation of *probes* in, for example, a hybridization assay. In contrast, as recited in claim 1, the targets themselves are synthesized.

As illustrated in Scheme C, one embodiment of claim 1 includes providing a nucleic acid template and providing nucleotides that have certain characteristics<sup>1</sup>, such that when the nucleotides are polymerized to form an unstructured nucleic acid, the nucleotides do not form an *intramolecular* base pair. Support for the illustration in Scheme C can be found in the specification at least at FIGs. 8A-8C and their attendant descriptions in the originally filed specification. This is novel and nonobvious in view of *Kutyavin*. Applicant discovered the following:

[T]here is a correlation between the predicted stability of the polynucleotide's secondary structure and its efficiency as a target in the single-base extension reaction. HP28 is a more efficient target than HP26 which, in turn, is a more efficient target than HP21 suggesting that *intramolecular target structures near a primer binding site can effect the polymerase extension efficiency at that site*. Thus because this same trend is exaggerated for the D [2-amino-2'-deoxyadenosine-5'-triphosphate (dDTP)] and S [2-thiothymidine-5'-triphosphate (2-thioTTP)]-containing polynucleotides, the results support the conclusion that the modifications do indeed alter the secondary structure of the polynucleotide targets. ... [T]hese results clearly demonstrate that *incorporating the 2-aminoadenosine and 2-thiothymidine nucleotide pair into a polynucleotide sequence increases the utility of the polynucleotide in hybridization-based assays*.

<sup>1</sup> Note that Scheme C uses the term "modified nucleotides." This term is merely for purposes of illustrating the concepts of Scheme C, as one embodiment, and not intended to limit the scope of claim 1. The term "collection of nucleotides" in claim 1 should be given its full scope and meaning in accordance with the specification as originally filed.

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*Specification* at last paragraph. Thus, not all the steps/features of claim 1 are taught or suggested by *Kutyavin*.

The Examiner argues in the Advisory Action that the distinction between inter-molecular and intra-molecular base complementarity is only shown in the context of the target sequence. *See Advisory Action* at 4. The present claims recite "[a] method of synthesizing an unstructured nucleic acid..." followed by multiple steps. Without admitting to the accuracy of the Examiner's argument, even if it were true, simply providing a target with the desired characteristics does not anticipate a method of synthesizing the unstructured nucleic acid by the steps of claim 1. Therefore, for at least this reason also, *Kutyavin* does not anticipate claim 1.

For at least these reasons, Applicant therefore respectfully requests that the rejection of claim 1 be withdrawn.

**C. Claims 25-34 are Patentable over *Vivekananda* and *Kutyavin***

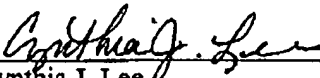
If independent claim 1 is allowable over the prior art of record, then its respective dependent claims 25-35 are also allowable as a matter of law, because these dependent claims contain all features/elements/steps of their respective independent claim. *See, e.g., In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). Additionally and notwithstanding the foregoing reasons for the allowability of claim 1, the dependent claims recite further features and/or combinations of features, as apparent by examination of the claims themselves, that are patentably distinct from the prior art of record. Hence, there are other reasons why these dependent claims are allowable over *Vivekananda* and *Kutyavin*.

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In summary, it is Applicant's position that Applicant's claims are patentable over the applied prior art references and that the rejection of these claims should be withdrawn. Appellant therefore respectfully requests that the Board of Appeals overturn the Examiner's rejection and allow Applicant's pending claims.

Respectfully submitted,

By:

  
Cynthia J. Lee

Registration No. 46,033

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**VIII. Claims Appendix under 37 C.F.R. § 41.37(c)(1)(viii)**

The following are the claims that are involved in this Appeal.

1. A method of synthesizing an unstructured nucleic acid, the method comprising steps of:

providing a nucleic acid template strand including a first template sequence element and a second template sequence element that is substantially complementary to the first template sequence element;

providing a collection of nucleotides sufficient to synthesize a nucleic acid strand complementary to at least a portion of the template nucleic acid strand, which portion includes the first and second template sequence elements, the collection including at least a first complementary nucleotide that hybridizes with a first residue within the first sequence element on the template strand and a second complementary nucleotide that hybridizes with a second residue within the second sequence element on the template strand, wherein the first and second residues are complementary to one another but the first and second nucleotides have a reduced ability to form a stable hydrogen bonded base pair; and

contacting the template and the nucleotides with an RNA polymerase enzyme characterized by an ability to polymerize the nucleotides under conditions and for a time sufficient to synthesize an unstructured nucleic acid in which said first complementary nucleotide and said second complementary nucleotide of the unstructured nucleic acid do not form an intramolecular base pair.

2-24. (Canceled)

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25. (Previously added) The method of claim 1, wherein said first residue within said first sequence element on the template strand is adenine and said second residue within said second sequence element on the template strand is thymidine;

and wherein said first complementary nucleotide is 2-thiothymidine 5'-triphosphate and said second complementary nucleotide is 2-amino-2'-deoxyadenosine 5'-triphosphate.

26. (Previously added) The method of claim 1, wherein said first residue within said first sequence element on the template strand is adenine and said second residue within said second sequence element on the template strand is uridine;

and wherein said first complementary nucleotide is 2-thiothymidine 5'-triphosphate and said second complementary nucleotide is 2-amino-2'-deoxyadenosine 5'-triphosphate.

27. (Previously added) The method of claim 1, wherein said first residue within the first sequence element on the template strand is guanidine and said second residue within said second sequence element on the template strand is cytidine;

and wherein said first complementary nucleotide is 2'-deoxypyrrolo-pyrimidine 5'-triphosphate and said second complementary nucleotide is 2'-deoxyinosine 5'-triphosphate.

28. (Previously added) The method of claim 1, wherein said first residue within said first sequence element on the template strand is inosine and said second residue within said second sequence element on the template strand is cytidine;

and wherein said first complementary nucleotide is 2-thio-2'-deoxycytidine 5'-triphosphate and said second complementary nucleotide is 2'-deoxyguanosine 5'-triphosphate.

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29. (Previously added) The method of claim 1, wherein said first residue within said first sequence element on the template strand is adenine and said second residue within said second sequence element on the template strand is thymidine;

and wherein said first complementary nucleotide is 2-thiouridine 5'-triphosphate and said second complementary nucleotide is 2-aminoadenosine 5'-triphosphate.

30. (Previously added) The method of claim 1, wherein said first residue within said first sequence element on the template strand is adenine and said second residue within said second sequence element on the template strand is uridine;

and wherein said first complementary nucleotide is 2-thiouridine 5'-triphosphate and said second complementary nucleotide is 2-aminoadenosine 5'-triphosphate.

31. (Previously added) The method of claim 1, wherein said first residue within the first sequence element on the template strand is guanidine and said second residue within said second sequence element on the template strand is cytidine;

and wherein said first complementary nucleotide is pyrrolo-pyrimidine 5'-triphosphate and said second complementary nucleotide is inosine 5'-triphosphate.

32. (Previously added) The method of claim 1, wherein said first residue within said first sequence element on the template strand is inosine and said second residue within said second sequence element on the template strand is cytidine;

and wherein said first complementary nucleotide is 2-thiocytidine 5'-triphosphate and said second complementary nucleotide is adenosine 5'-triphosphate.

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33. (Previously added) The method of claim 1, wherein said unstructured nucleic acid is at least 40 nucleotides in length.
34. (Previously added) The method of claim 1, wherein said unstructured nucleic acid is at least 100 nucleotides in length.
35. (Previously added) The method of claim 1, wherein said unstructured nucleic acid is at least 500 nucleotides in length.

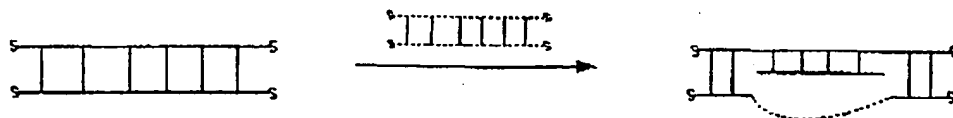
*Application No: Sampson.**Serial No.: 09/358,141***IX. Evidence Appendix under 37 C.F.R. § 41.37(c)(1)(ix)**

Attached hereto as evidence is Exhibit A, page 1 of 1. Exhibit A was submitted by Applicant in a Response filed August 15, 2005. The Examiner considered Exhibit A and entered it into the record, as indicated in the Advisory Action mailed December 22, 2005.

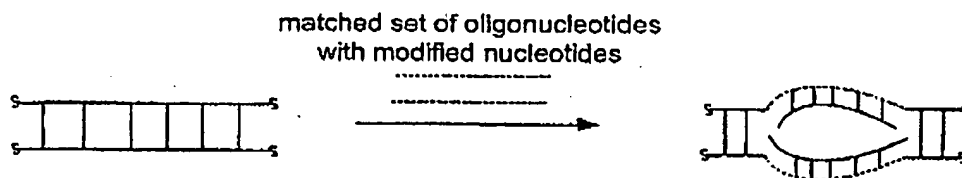


*Application No: Sampson**Serial No.: 09/358,141***X. Related Proceedings Appendix under 37 C.F.R. § 41.37(c)(1)(x)**

There are no related proceedings to be considered in this Appeal. Therefore, no such proceedings are identified in this Appendix.



SCHEME A - PRIOR TO KUTYAVIN



SCHEME B - KUTYAVIN

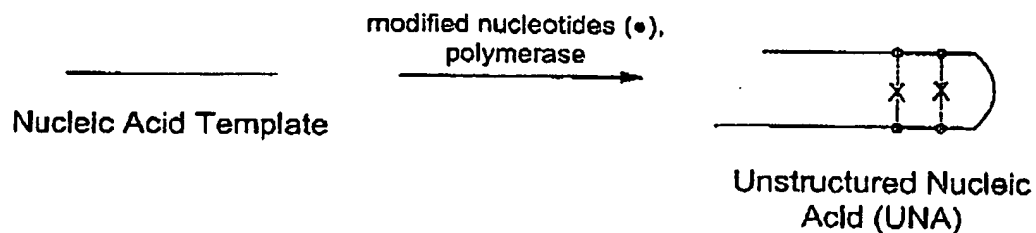
SCHEME C - ONE EMBODIMENT OF  
CLAIM 1

EXHIBIT A  
PAGE 1 OF 1